



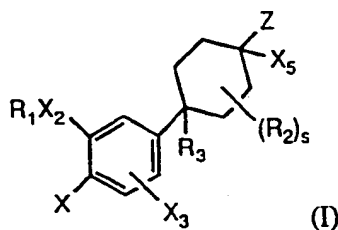
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<p>(21) International Application Number: PCT/US93/01988 (22) International Filing Date: 5 March 1993 (05.03.93) (30) Priority data: 07/862,112 2 April 1992 (02.04.92) US 07/968,760 30 October 1992 (30.10.92) US (60) Parent Applications or Grants (63) Related by Continuation US 07/968,760 (CIP) Filed on 30 October 1992 (30.10.92) US 07/862,112 (CIP) Filed on 2 April 1992 (02.04.92) (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).</p>	<p>(72) Inventor; and (75) Inventor/Applicant (for US only) : CHRISTENSEN, Siegfried, B., IV [US/US]; 2216 Race Street, Philadelphia, PA 19103 (US). (74) Agents: KANAGY, James, M. et al.; SmithKline Beecham Corporation, Corporate Patents - U.S., UW2220, 709 Swedeland Road, P.O. Box 1538, King of Prussia, PA 19406-0939 (US). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, RO, RU, SD, SE, SK, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG). Published With international search report.</p>	

(54) Title: COMPOUNDS USEFUL FOR TREATING ALLERGIC AND INFLAMMATORY DISEASES



(57) Abstract

Novel cyclohexane-ylidene derivatives of formula (I) are described. These compounds inhibit the production of Tumor Necrosis Factor and are useful in the treatment of disease states mediated or exacerbated by TNF production. These compounds are also useful in the mediation or inhibition of enzymatic or catalytic activity of phosphodiesterase IV and are therefore useful in the treatment of disease states in need of mediation or inhibition thereof.

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"Compounds Useful for Treating Allergic and Inflammatory Diseases"

Field of Invention

The present invention relates to novel compounds, pharmaceutical compositions containing these compounds, and their use in treating allergic and inflammatory diseases and
5 for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

10 Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of the disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

15 One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs; [Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17-29, 1973]. When the appropriate agonist binds to specific cell surface receptors, adenylate
20 cyclase is activated, which converts Mg^{+2} -ATP to cAMP at an accelerated rate.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway smooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of
25 basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit phosphodiesterase should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is
30 hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cAMP breakdown in airway smooth muscle and inflammatory cells. [Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-
35 asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd., 1989]. Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case *in vivo*.

Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E₂ and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

5 The compounds of this invention also inhibit the production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory
10 distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar
15 tissue formation, Crohn's disease, ulcerative colitis, or pyresis, in addition to a number of autoimmune diseases, such as multiple sclerosis, autoimmune diabetes and systemic lupus erythematosus.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2
20 and HIV-3. As a consequence of HIV infection, T-cell-mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Viruses such as HIV-1 or HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T
25 lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication.

Cytokines, specifically TNF, are implicated in activated T-cell-mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by inhibition of cytokine production,
30 notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are
35 targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg *et al.*, The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, 1989]. Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli *et al.*, Proc. Natl. Acad.

Sci., 87:782-784, 1990], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

5 TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus, adenovirus, and the herpes virus for similar reasons as those noted.

10 TNF is also associated with yeast and fungal infections. Specifically *Candida albicans* has been shown to induce TNF production *in vitro* in human monocytes and natural killer cells. [See Riipi *et al.*, Infection and Immunity, 58(9):2750-54, 1990; and Jafari *et al.*, Journal of Infectious Diseases, 164:389-95, 1991. See also Wasan *et al.*, Antimicrobial Agents and Chemotherapy, 35,(10):2046-48, 1991; and Luke *et al.*, Journal of Infectious Diseases, 162:211-214, 1990].

15 The ability to control the adverse effects of TNF is furthered by the use of the compounds which inhibit TNF in mammals who are in need of such use. There remains a need for compounds which are useful in treating TNF-mediated disease states which are exacerbated or caused by the excessive and/or unregulated production of TNF.

Summary of the Invention

20 This invention relates to the novel compounds of Formula (I), as shown below, useful in the mediation or inhibition of the enzymatic activity (or catalytic activity) of phosphodiesterase IV (PDE IV). The novel compounds of Formula (I) also have Tumor Necrosis Factor (TNF) inhibitory activity.

 This invention also relates to the pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

25 The invention also relates to a method of mediation or inhibition of the enzymatic activity (or catalytic activity) of PDE IV in mammals, including humans, which comprises administering to a mammal in need thereof an effective amount of a compound of Formula (I), as shown below.

30 The invention further provides a method for the treatment of allergic and inflammatory disease which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (I).

 The invention also provides a method for the treatment of asthma which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (I).

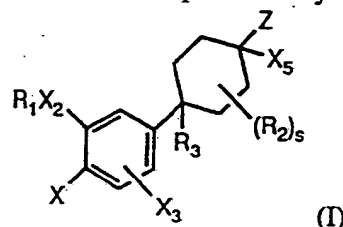
35 This invention also relates to a method of inhibiting TNF production in a mammal, including humans, which method comprises administering to a mammal in need of such treatment, an effective TNF inhibiting amount of a compound of Formula (I). This method may be used for the prophylactic treatment or prevention of certain TNF mediated disease states amenable thereto.

This invention also relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), which comprises administering to such human an effective TNF inhibiting amount of a compound of Formula (I).

The compounds of Formula (I) are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*.

The compounds of Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*.

The compounds of this invention are represented by Formula (I):



wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;

m is 0 to 2;

n is 1 to 4;

r is 1 to 6;

R_4 and R_5 are independently selected from hydrogen or C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy C_{1-3} alkyl, halo substituted aryloxy C_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2; or

b) when R_6 is hydroxyl, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2 , halogen, nitro, NR_4R_5 , or formyl amine;

Y is O or $S(O)_m$;

- m' is 0, 1, or 2;
 X_2 is O or NR_8 ;
 X_3 is hydrogen or X;
 R_2 is independently selected from $-CH_3$ or $-CH_2CH_3$ optionally substituted by 1 or
 5 more halogens;
 s is 0 to 4;
 R_3 is hydrogen, halogen, C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, halo-substituted C_{1-4} alkyl, $-CH=CR_8R_8'$, cyclopropyl optionally substituted by R_8' , CN, OR_8 , CH_2OR_8 , NR_8R_{10} , $CH_2NR_8R_{10}$, $C(Z')H$, $C(O)OR_8$, $C(O)NR_8R_{10}$, or $C\equiv CR_8$;
 10 Z' is O, NR_9 , NOR_8 , NCN , $C(-CN)_2$, CR_8CN , CR_8NO_2 , $CR_8C(O)OR_8$, $CR_8C(O)NR_8R_8$, $C(-CN)NO_2$, $C(-CN)C(O)OR_9$, or $C(-CN)C(O)NR_8R_8$;
 Z is $CR_8R_8OR_{14}$, $CR_8R_8OR_{15}$, $CR_8R_8SR_{14}$, $CR_8R_8SR_{15}$, $CR_8R_8S(O)_{m'}R_7$, $CR_8R_8NR_{10}R_{14}$, $CR_8R_8NR_{10}S(O)_2NR_{10}R_{14}$, $CR_8R_8NR_{10}S(O)_2R_7$, $CR_8R_8NR_{10}C(Y')R_{14}$, $CR_8R_8NR_{10}C(O)OR_7$, $CR_8R_8NR_{10}C(Y')NR_{10}R_{14}$,
 15 $CR_8R_8NR_{10}C(NCN)NR_{10}R_{14}$, $CR_8R_8NR_{10}C(CR_4NO_2)NR_{10}R_{14}$, $CR_8R_8NR_{10}C(NCN)SR_9$, $CR_8R_8NR_{10}C(CR_4NO_2)SR_9$, $CR_8R_8C(O)OR_{14}$, $CR_8R_8C(Y')NR_{10}R_{14}$, $CR_8R_8C(NR_{10})NR_{10}R_{14}$, CR_8R_8CN , CR_8R_8 (tetrazolyl), CR_8R_8 (imidazolyl), CR_8R_8 (imidazolidinyl), CR_8R_8 (pyrazolyl), CR_8R_8 (thiazolyl), CR_8R_8 (thiazolidinyl), CR_8R_8 (oxazolyl), CR_8R_8 (oxazolidinyl), CR_8R_8 (triazolyl),
 20 CR_8R_8 (isoxazolyl), CR_8R_8 (oxadiazolyl), CR_8R_8 (thiadiazolyl), CR_8R_8 (morpholinyl), CR_8R_8 (piperidinyl), CR_8R_8 (piperazinyl), CR_8R_8 (pyrrolyl), $CR_8R_8C(NOR_8)R_{14}$, $CR_8R_8C(NOR_{14})R_8$, $CR_8R_8NR_{10}C(NR_{10})SR_9$, $CR_8R_8NR_{10}C(NR_{10})NR_{10}R_{14}$, $CR_8R_8NR_{10}C(O)C(O)NR_{10}R_{14}$, or $CR_8R_8NR_{10}C(O)C(O)OR_{14}$;
 X_5 is H, R_9 , OR_8 , CN, $C(O)R_8$, $C(O)OR_8$, $C(O)NR_8R_8$, or NR_8R_8 ; or Z and X_5
 25 together is $-CR_8R_8O-$;
 Y' is O or S;
 R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, $-F$, $-Br$, $-Cl$, $-NO_2$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-C(O)OR_8$, $-OR_8$, $-CN$, $-C(O)NR_{10}R_{11}$,
 30 $-OC(O)NR_{10}R_{11}$, $-OC(O)R_8$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_{m'}R_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;
 35 q is 0, 1, or 2;
 R_{12} is C_{3-7} cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;
 R_8 is independently selected from hydrogen or R_9 ;

R₈ is R₈ or fluorine;

R₉ is C₁₋₄ alkyl optionally substituted by one to three fluorines;

R₁₀ is OR₈ or R₁₁;

R₁₁ is hydrogen, or C₁₋₄ alkyl optionally substituted by one to three fluorines; or

- 5 when R₁₀ and R₁₁ are as NR₁₀R₁₁ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S;

- 10 R₁₃ is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C₁₋₂ alkyl groups;

R₁₄ is hydrogen or R₇; or when R₁₀ and R₁₄ are as NR₁₀R₁₄ they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;

- 15 R₁₅ is C(O)R₁₄, C(O)NR₈R₁₄, S(O)₂NR₈R₁₄, S(O)₂R₇;

provided that:

f) when R₁₂ is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1;

- 20 g) when X₂R₁ is OCF₂H or OCF₃, X is F, OCF₂H or OCF₃, X₃ is H, s is zero, X₅ is H, Z is CH₂OR₁₄, and R₁₄ is C₁₋₇ unsubstituted alkyl, then R₃ is other than H; or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

- 25 This invention relates to the novel compounds of Formula (I), and to pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent. This invention also relates to a method of mediating or inhibiting the enzymatic activity (or catalytic activity) of PDE IV in a mammal in need thereof and to inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

- 30 Phosphodiesterase IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases including: asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult
35 respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus, [Kidney Int., 37:362, 1990; Kidney Int., 35:494, 1989] and central nervous system disorders such as depression and multi-infarct dementia.

The compounds of Formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production in

vivo. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I).

The compounds of Formula (I) may also be used in association with the veterinary treatment of animals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of Formula (I) are also useful in the treatment of yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis. Additionally, the compounds of Formula (I) may be administered in conjunction with other drugs of choice for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymyxins, such as Polymycin B, the class of compounds called the imidazoles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

The co-administration of the anti-fungal agent with a compound of Formula (I) may be in any preferred composition for that compound such as is well known to those skilled in the art, for instance the various Amphotericin B formulations. Co-administration of an anti-fungal agent with a compound of Formula (I) may mean simultaneous administration or in practice, separate administration of the agents to the mammal but in a consecutive manner. In particular, the compounds of Formula (I) may be co-administered with a formulation of Amphotericin B, notably for systemic fungal infections. The preferred organism for treatment is the *Candida* organism. The compounds of Formula (I) may be co-administered in a similar manner with anti-viral or anti-bacterial agents.

The compounds of Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of Formula (I) to a mammal in need of such treatment. Preferably, a compound of Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

Preferred compounds are as follows:

When R₁ for the compounds of Formula (I) is an alkyl substituted by 1 or more halogens, the halogens are preferably fluorine and chlorine, more preferably a C₁₋₄ alkyl substituted by 1 or more fluorines. The preferred halo-substituted alkyl chain length is one or two carbons, and most preferred are the moieties -CF₃, -CH₂F, -CHF₂, -CF₂CHF₂, -CH₂CF₃, and -CH₂CHF₂. Preferred R₁ substituents for the compounds of Formula (I) are CH₂-cyclopropyl, CH₂-C₅₋₆ cycloalkyl, C₄₋₆ cycloalkyl, C₇₋₁₁ polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C₁₋₂ alkyl optionally substituted by 1 or more fluorines, -(CH₂)₁₋₃C(O)O(CH₂)₀₋₂CH₃, -(CH₂)₁₋₃O(CH₂)₀₋₂CH₃, and -(CH₂)₂₋₄OH.

When the R₁ term contains the moiety (CR₄R₅), the R₄ and R₅ terms are independently hydrogen or alkyl. This allows for branching of the individual methylene units as (CR₄R₅)_n or (CR₄R₅)_m; each repeating methylene unit is independent of the other, e.g., (CR₄R₅)_n wherein n is 2 can be -CH₂CH(-CH₃)-, for instance. The individual hydrogen atoms of the repeating methylene unit or the branching hydrocarbon can optionally be substituted by fluorine independent of each other to yield, for instance, the preferred R₁ substitutions, as noted above.

When R₁ is a C₇₋₁₁ polycycloalkyl, examples are bicyclo[2.2.1]-heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo[5.2.1.0^{2,6}]decyl, etc. additional examples of which are described in Saccamano *et al.*, WO 87/06576, published 5 November 1987, whose disclosure is incorporated herein by reference in its entirety.

Z is preferably CR₈R₈OR₁₄, CR₈R₈OR₁₅, CR₈R₈SR₁₄, CR₈R₈SR₁₅, CR₈R₈S(O)_mR₇, CR₈R₈NR₁₀R₁₄, CR₈R₈NS(O)₂NR₁₀R₁₄, CR₈R₈NS(O)₂R₇, CR₈R₈NR₁₀C(O)R₁₄, CR₈R₈NR₁₀C(O)OR₇, CR₈R₈NR₁₀C(O)NR₁₀R₁₄, CR₈R₈NR₁₀C(NCN)NR₁₀R₁₄, CR₈R₈NR₁₀C(CR₄NO₂)NR₁₀R₁₄, CR₈R₈NR₁₀C(NCN)SR₉, CR₈R₈NR₁₀C(CR₄NO₂)SR₉, CR₈R₈C(O)OR₁₄, CR₈R₈C(O)NR₁₀R₁₄, CR₈R₈C(NR₁₀)NR₁₀R₁₄, CR₈R₈CN, CR₈R₈C(NOR₈)R₁₄, CR₈R₈C(NOR₁₄)R₈, CR₈R₈NR₁₀C(NR₁₀)SR₉, CR₈R₈NR₁₀C(NR₁₀)NR₁₀R₁₄, CR₈R₈NR₁₀C(O)C(O)NR₁₀R₁₄, or CR₈R₈NR₁₀C(O)C(O)OR₁₄; most preferred are those compounds wherein the R₈ group of Z is H and the R₁₄ group of Z is R₄.

Preferred X₅ groups are H, OH, OCH₃, CN, C(O)R₈, C(O)OH, C(O)OCH₃, C(O)NH₂, CON(CH₃)₂, NH₂, or N(CH₃)₂. The most preferred groups are H, OH, CN, C(O)OH, C(O)NH₂ or NH₂.

The preferred group wherein Z and X₅ together is -CR₈R₈CO- is -CH₂CO-.

Preferred X groups for Formula (I) are those wherein X is YR₂ and Y is oxygen. The preferred X₂ group for Formula (I) is that wherein X₂ is oxygen. The preferred X₃ group for Formula (I) is that wherein X₃ is hydrogen. Preferred R₂ groups, where applicable, is a C₁₋₂ alkyl optionally substituted by 1 or more halogens. The halogen atoms are preferably fluorine and chlorine, more preferably fluorine. More preferred R₂ groups are those wherein

R₂ is methyl, or the fluoro-substituted alkyls, specifically a C₁₋₂ alkyl, such as a -CF₃, -CHF₂, or -CH₂CHF₂ moiety. Most preferred are the -CHF₂ and -CH₃ moieties.

Preferred R₃ moieties are C(O)NH₂, C≡CR₈, CH₂NHC(O)C(O)NH₂, CN, C(Z')H, CH₂OH, CH₂F, CF₂H, and CF₃. More preferred are C≡CH and CN. Z' is preferably O or NOR₈.

Preferred R₇ moieties include optionally substituted -(CH₂)₁₋₂(cyclopropyl), -(CH₂)₀₋₂(cyclobutyl), -(CH₂)₀₋₂(cyclopentyl), -(CH₂)₀₋₂(cyclohexyl), -(CH₂)₀₋₂(2-, 3- or 4-pyridyl), (CH₂)₁₋₂(2-imidazolyl), (CH₂)₂(4-morpholinyl), (CH₂)₂(4-piperazinyl), (CH₂)₁₋₂(2-thienyl), (CH₂)₁₋₂(4-thiazolyl), and (CH₂)₀₋₂phenyl;

Preferred rings when R₁₀ and R₁₁ in the moiety -NR₁₀R₁₁ together with the nitrogen to which they are attached form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S include, but are not limited to 1-imidazolyl, 2-(R₈)-1-imidazolyl, 1-pyrazolyl, 3-(R₈)-1-pyrazolyl, 1-triazolyl, 2-triazolyl, 5-(R₈)-1-triazolyl, 5-(R₈)-2-triazolyl, 5-(R₈)-1-tetrazolyl, 5-(R₈)-2-tetrazolyl, 1-tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, 4-(R₈)-1-piperazinyl, or pyrrolyl ring.

Preferred rings when R₁₀ and R₁₄ in the moiety -NR₁₀R₁₄ together with the nitrogen to which they are attached may form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 2-triazolyl, 1-tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, and pyrrolyl. The respective rings may be additionally substituted, where applicable, on an available nitrogen or carbon by the moiety R₇ as described herein for Formula (I). Illustrations of such carbon substitutions includes, but are not limited to, 2-(R₇)-1-imidazolyl, 4-(R₇)-1-imidazolyl, 5-(R₇)-1-imidazolyl, 3-(R₇)-1-pyrazolyl, 4-(R₇)-1-pyrazolyl, 5-(R₇)-1-pyrazolyl, 4-(R₇)-2-triazolyl, 5-(R₇)-2-triazolyl, 4-(R₇)-1-triazolyl, 5-(R₇)-1-triazolyl, 5-(R₇)-1-tetrazolyl, and 5-(R₇)-2-tetrazolyl. Applicable nitrogen substitution by R₇ includes, but is not limited to, 1-(R₇)-2-tetrazolyl, 2-(R₇)-1-tetrazolyl, 4-(R₇)-1-piperazinyl. Where applicable, the ring may be substituted one or more times by R₇.

Preferred groups for NR₁₀R₁₄ which contain a heterocyclic ring are 5-(R₁₄)-1-tetrazolyl, 2-(R₁₄)-1-imidazolyl, 5-(R₁₄)-2-tetrazolyl, or 4-(R₁₄)-1-piperazinyl.

Preferred rings for R₁₃ include (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl), or (2-, 4-, or 5-imidazolidinyl).

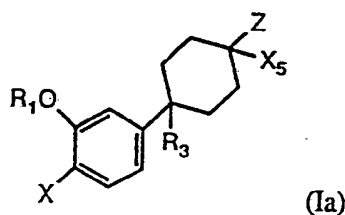
When the R₇ group is optionally substituted by a heterocyclic ring such as imidazolyl, pyrazolyl, triazolyl, tetrazolyl, or thiazolyl, the heterocyclic ring itself may be optionally substituted by R₈ either on an available nitrogen or carbon atom, such as 1-(R₈)-2-imidazolyl, 1-(R₈)-4-imidazolyl, 1-(R₈)-5-imidazolyl, 1-(R₈)-3-pyrazolyl,

1-(R₈)-4-pyrazolyl, 1-(R₈)-5-pyrazolyl, 1-(R₈)-4-triazolyl, or 1-(R₈)-5-triazolyl. Where applicable, the ring may be substituted one or more times by R₈.

Preferred are those compounds of Formula (I) wherein R₁ is -CH₂-cyclopropyl, -CH₂-C₅₋₆ cycloalkyl, -C₄₋₆ cycloalkyl, tetrahydrofuran-3-yl, (3- or 4-cyclopentenyl), benzyl or -C₁₋₂ alkyl optionally substituted by 1 or more fluorines, and -(CH₂)₂₋₄ OH; R₂ is methyl or fluoro-substituted alkyl, R₃ is CN or C≡CR₈; and X is YR₂.

Most preferred are those compounds wherein R₁ is -CH₂-cyclopropyl, cyclopentyl, methyl or CF₂H; R₃ is CN or C≡CH; X is YR₂; Y is oxygen; X₂ is oxygen; X₃ is hydrogen; and R₂ is CF₂H or methyl.

A preferred subgenus of the compounds of Formula (I) is the compounds of Formula (Ia)



wherein:

R₁ is CH₂-cyclopropyl, CH₂-C₅₋₆ cycloalkyl, C₄₋₆ cycloalkyl, C₇₋₁₁ polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C₁₋₂ alkyl optionally substituted by 1 or more fluorines, -(CH₂)₁₋₃C(O)O(CH₂)₀₋₂CH₃, -(CH₂)₁₋₃O(CH₂)₀₋₂CH₃, and -(CH₂)₂₋₄OH;

X is YR₂, halogen, nitro, NR₄R₅, or formyl amine;

Y is O or S(O)_{m'};

m' is 0, 1, or 2;

R₂ is -CH₃ or -CH₂CH₃ optionally substituted by 1 or more halogens;

R₃ is hydrogen, C₁₋₄ alkyl, CH₂NHC(O)C(O)NH₂, halo-substituted C₁₋₄ alkyl, CN, CH₂OR₈, C(Z')H, C(O)OR₈, C(O)NR₈R₁₀, or C≡CR₈;

Z' is O or NOR₈;

Z is CR₈R₈OR₁₄, CR₈R₈OR₁₅, CR₈R₈SR₁₄, CR₈R₈SR₁₅, CR₈R₈S(O)_mR₇, CR₈R₈NR₁₀R₁₄, CR₈R₈NS(O)₂NR₁₀R₁₄, CR₈R₈NS(O)₂R₇, CR₈R₈NR₁₀C(Y')R₁₄, CR₈R₈NR₁₀C(O)OR₇, CR₈R₈NR₁₀C(Y')NR₁₀R₁₄, CR₈R₈NR₁₀C(NCN)NR₁₀R₁₄, CR₈R₈NR₁₀C(CR₄NO₂)NR₁₀R₁₄, CR₈R₈NR₁₀C(NCN)SR₉, CR₈R₈NR₁₀C(CR₄NO₂)SR₉, CR₈R₈C(Y')OR₁₄, CR₈R₈C(Y')NR₁₀R₁₄, CR₈R₈C(NR₁₀)NR₁₀R₁₄, CR₈R₈CN, CR₈R₈C(NOR₈)R₁₄, CR₈R₈C(NOR₁₄)R₈, CR₈R₈NR₁₀C(NR₁₀)SR₉, CR₈R₈NR₁₀C(NR₁₀)NR₁₀R₁₄, CR₈R₈NR₁₀C(O)C(O)NR₁₀R₁₄, or CR₈R₈NR₁₀C(O)C(O)OR₁₄;

X₅ is H, OR₈, CN, C(O)OR₈ or NR₈R₈; or Z and X₅ together is -CR₈R₈CO-;

Y' is O or S;

R₇ is -(CR₄R₅)_qR₁₂ or C₁₋₆ alkyl wherein the R₁₂ or C₁₋₆ alkyl group is optionally substituted one or more times by methyl or ethyl substituted by 1-3 fluorines, -F, -Br, -Cl,

- NO₂, -NR₁₀R₁₁, -C(O)R₈, -C(O)OR₈, -OR₈, -CN, -C(O)NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -OC(O)R₈, -NR₁₀C(O)NR₁₀R₁₁, -NR₁₀C(O)R₁₁, -NR₁₀C(O)OR₉, -NR₁₀C(O)R₁₃, -C(NR₁₀)NR₁₀R₁₁, -C(NCN)NR₁₀R₁₁, -C(NCN)SR₉, -NR₁₀C(NCN)SR₉, -NR₁₀C(NCN)NR₁₀R₁₁, -NR₁₀S(O)₂R₉, -S(O)_mR₉, -NR₁₀C(O)C(O)NR₁₀R₁₁,
 5 -NR₁₀C(O)C(O)R₁₀, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;
 q is 0, 1, or 2;
 R₁₂ is C₃-C₇ cycloalkyl, (2-, 3- or 4-pyridyl), (1- or 2-imidazolyl), piperazinyl, morpholinyl, (2- or 3-thienyl), (4- or 5-thiazolyl), or phenyl;
 R₈ is independently selected from hydrogen or R₉;
 10 R₉ is C₁₋₄ alkyl optionally substituted by one to three fluorines;
 1 R₁₀ is OR₈ or R₁₁;
 R₁₁ is hydrogen or C₁₋₄ alkyl optionally substituted by one to three fluorines; or when R₁₀ and R₁₁ are as NR₁₀R₁₁ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O,
 15 N, or S;
 R₁₃ is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C₁₋₂ alkyl groups;
 20 R₁₄ is hydrogen or R₇; or when R₁₀ and R₁₄ are as NR₁₀R₁₄ they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;
 R₁₅ is C(O)R₁₄, C(O)NR₈R₁₄, S(O)₂NR₈R₁₄, S(O)₂R₇;
 provided that:
 25 a) when R₁₂ is N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, or N-morpholinyl, then q is not 1;
 b) when R₁ is CF₂H or CF₃, X is F, OCF₂H or OCF₃, X₅ is H, Z is CH₂OR₁₄, and R₁₄ is C₁₋₇ unsubstituted alkyl, then R₃ is other than H;
 or the pharmaceutically acceptable salts thereof.
 30 Preferred compounds of Formula (I) are:
 methyl 2-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-yl]acetate;
 cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methanol;
 cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methylamine;
 35 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1,1-diyl]oxirane;
 cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexan-1-yl]methanol;

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1,1-diyl]oxirane; and

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexan-1-yl]methanol.

5 Some of the compounds of Formula (I) may exist in both racemic and optically active forms; some may also exist in distinct diastereomeric forms. All of these compounds are considered to be within the scope of the present invention. Therefore another aspect of the present invention is the administration of either a racemate, a single enantiomeric form, a single diastereomeric form, or mixtures thereof.

10

Definitions

The terms "C₁₋₃ alkyl", "C₁₋₄ alkyl", "C₁₋₆ alkyl" or "alkyl" include both straight or branched chain radicals of 1 to 10, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl, and the like. "Alkenyl" includes both straight or branched chain radicals of 1 to 6 carbon lengths, unless the chain length is limited thereto, including but not limited to vinyl, 1-propenyl, 2-propenyl, 2-propynyl, or 3-methyl-2-propenyl. "Cycloalkyl" or "cycloalkyl alkyl" includes radicals of 3-7 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl, or cyclohexyl. "Aryl" or "aralkyl", unless specified otherwise, means an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl, or naphthyl. Preferably the aryl is monocyclic, i.e., phenyl. The alkyl chain is meant to include both straight or branched chain radicals of 1 to 4 carbon atoms. "Heteroaryl" means an aromatic ring system containing one or more heteroatoms, such as imidazolyl, triazolyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, pyrrolyl, furanyl, or thienyl. "Halo" means chloro, fluoro, bromo, or iodo.

25 By the phrase "inhibiting the production of IL-1" or "inhibiting the production of TNF" means:

a) a decrease of excessive *in vivo* IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels by inhibition of the *in vivo* release of IL-1 by all cells, including but not limited to monocytes or macrophages;

30 b) a down regulation, at the translational or transcriptional level, of excessive *in vivo* IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of IL-1 or TNF levels as a posttranslational event.

35 By the term "TNF mediated disease or disease states" is meant any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF- β (also known as lymphotoxin) has close structural homology

with TNF- α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF- α and TNF- β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise. Preferably TNF- α is inhibited.

5 "Cytokine" means any secreted polypeptide that affects the functions of cells, and is a molecule which modulates interactions between cells in immune, inflammatory, or hematopoietic responses. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage
10 and/or monocyte, but many other cells produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes, and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines for the present invention include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8),
15 Tumor Necrosis Factor-alpha (TNF- α) and Tumor Necrosis Factor-beta (TNF- β).

The cytokine inhibited by the present invention for use in the treatment of a HIV-infected human must be a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication, and/or (b) any cytokine-mediated disease associated problem such as
20 cachexia or muscle degeneration. Preferably, his cytokine is TNF- α .

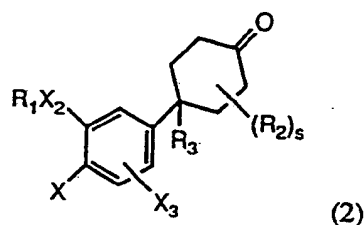
The cytokine inhibited by the present invention for use in the treatment of a HIV-infected human must be a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication, and/or (b) any cytokine-mediated disease associated problem such as cachexia or
25 muscle degeneration. Preferably, his cytokine is TNF- α .

All of the compounds of Formula (I) are useful in the method of inhibiting the production of TNF, preferably by macrophages, monocytes or macrophages and monocytes, in a mammal, including humans, in need thereof. All of the compounds of Formula (I) are useful in the method of inhibiting or mediating the enzymatic or catalytic activity of PDE IV
30 and in treatment of disease states mediated thereby.

METHODS OF PREPARATION:

Preparing compounds of Formula (I) can be accomplished by one of skill in the art according to the procedures outlined in the Examples, *infra*. The preparation of any
35 remaining compounds of Formula (I) not described therein may be prepared by the analogous processes disclosed herein which comprise:

a) for compounds of Formula (I) wherein R₃ is other than C(=Z)H and wherein Z is CH₂COOCH₃, reacting a compound of Formula (2)



where R_1 represents R_1 as defined in relation to Formula (I) or a group convertible to R_1 and X and X_3 represent X and X_3 as defined in relation to Formula (I) or a group convertible to X or X_3 and R_3 represents R_3 as defined in relation to Formula (I) or a group convertible to R_3 , with a stabilized acetate anion, such as sodium trimethylphosphonoacetate or lithium ethyl (trimethylsilyl)acetate, in a suitable non-reacting solvent, such as 1,2-dimethoxyethane or tetrahydrofuran, followed by reduction of the resulting ethylidene intermediate with, e.g., hydrogen and a suitable catalyst, to provide compounds of Formula (I) wherein R_3 is other than $C(=Z')H$ and wherein Z is CH_2COOCH_3 ; preparation of such compounds of Formula (I) wherein R_3 is $C(=Z')H$ proceed in an analogous fashion from the compound of Formula (2) wherein $=Z'$ is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by deprotection to the aldehyde and subsequent elaboration by standard procedures known to those of skill in the art to the remaining compounds of Formula (I) wherein Z' is other than O .

Saponification of the ester moiety of compounds of Formula (I) wherein R_3 is other than $COOR_8$ and wherein Z is CH_2COOCH_3 with, e.g., potassium hydroxide in methanol, provides compounds of Formula (I) wherein R_3 is other than $COOR_8$ and wherein Z is CH_2COOH ; preparation of such compounds of Formula (I) wherein R_3 is $COOR_8$ proceed in an analogous fashion from the compound of Formula (2) wherein $=Z'$ is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by deprotection to the aldehyde and subsequent elaboration by standard procedures known to those of skill in the art to the remaining compounds of Formula (I) wherein R_3 is $COOR_8$.

Compounds of Formula (I) wherein R_3 is other than $C(=Z')H$ and wherein Z is CH_2OH may be prepared in a wide variety of ways. For example, with appropriate manipulation of certain chemically sensitive functional groups, conversion of the ketone of the compounds of Formula (2) wherein R_1 represents R_1 as defined in relation to Formula (I) or a group convertible to R_1 and X and X_3 represents X and X_3 as defined in relation to Formula (I) or a group convertible to X or X_3 and R_3 represents R_3 as defined in relation to Formula (I) or a group convertible to R_3 and wherein R_3 is other than $C(=Z')H$, to the corresponding olefin by Wittig, Peterson or other olefination reactions followed by, e.g., hydroboration-oxidation; preparation of such compounds of Formula (I) wherein R_3 is $C(=Z')H$ proceed in an analogous fashion from the compound of Formula (2) wherein $=Z'$ is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by deprotection to the aldehyde and subsequent elaboration by standard procedures known to

those of skill in the art to the remaining compounds of Formula (I) wherein Z' is other than O.

Alternatively, compounds of Formula (I) may be obtained by homologation of the ketone of appropriate compounds of Formula (2) by, e.g., ketene thioacetal formation, subsequent hydrolysis to the aldehyde and reduction. Reductive amination with, e.g., ammonium formate and sodium cyanoborohydride in an alcoholic solvent, rather than reduction of such homologated aldehyde intermediates, provides the compounds of Formula (I) wherein R₃ is other than C(=Z')H and Z is CH₂NH₂; preparation of such compounds of Formula (I) wherein R₃ is C(=Z')H proceed in an analogous fashion from the homologated aldehyde intermediates wherein =Z' is an aldehyde protecting group, such as a dimethylacetal or a dioxolane, followed by deprotection to the R₃ aldehyde and subsequent elaboration by standard procedures known to those of skill in the art to the remaining compounds of Formula (I) wherein Z' is other than O.

It will be recognized that compounds of Formula (I) may exist in two distinct diastereomeric forms possessing distinct physical and biological properties; such isomers may be separated by standard chromatographic methods. Such isomers may be independently converted to other compounds of Formula (I) wherein Z is, e.g., CR₈R₈OR₁₄, CR₈R₈OR₁₅, CR₈R₈NR₁₃R₁₄, CR₈R₈NS(O)₂NR₁₃R₁₄, CR₈R₈NS(O)₂R₇, or CR₈R₈NR₁₃C(Y)R₁₄, by any of the wide variety of O and N alkylation or acylation procedures known to those of skill in the art.

For example, with proper manipulation of any chemically sensitive functional groups, compounds of Formula (I) wherein NR₁₃R₁₄ represent a ring, such as a 1- or 2-tetrazole, may be derived from reaction of an appropriate compound of Formula (I) wherein Z possesses a leaving group, L, as in CR₈R₈L, and L is a mesylate, tosylate, chloride or bromide, with the appropriate metal salt of HNR₁₃R₁₄, e.g., 5-(R₁₄)-tetrazole; the appropriate compound of Formula (I) wherein Z is mesylate, tosylate, Br or Cl, derived in turn from the appropriate compound of Formula (I) wherein Z is CR₈R₈OH. Using similar procedures but with the appropriate metal salt of SR₁₄ or SR₁₅, compounds of Formula (I) wherein Z is CR₈R₈SR₁₄ or CR₈R₈SR₁₅ may be prepared.

Compounds of Formula (2) may be prepared in turn by the processes described in co-pending application USSN 07/862,083 filed 2 April 1992.

The following examples are provided to illustrate how to make and use this invention. These examples are not intended to and should not be viewed as limiting the scope or practice of this invention in any way.

SYNTHETIC EXAMPLESEXAMPLE 14-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one(Intermediate of the Formula 2)

- 5 1a (3-Cyclopentyloxy-4-methoxyphenyl)acetonitrile To a solution of 3-cyclopentyloxy-4-methoxybenzaldehyde (20 g, 90.8 mmol) in acetonitrile (100 mL) was added lithium bromide (15 g, 173 mmol) followed by the dropwise addition of trimethylsilylchloride (17.4 mL, 137 mmol). After 15 min, the reaction mixture was cooled to 0°C, 1,1,3,3-tetramethyldisiloxane (26.7 mL, 151 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature. After stirring for 3h, the mixture was separated into two layers. The lower layer was removed, diluted with methylene chloride and filtered through Celite. The filtrate was concentrated under reduced pressure, dissolved in methylene chloride and refiltered. The solvent was removed *in vacuo* to provide a light tan oil. To a solution of this crude α -bromo-3-cyclopentyloxy-4-methoxytoluene in dimethylformamide (160 mL) under an argon atmosphere was added sodium cyanide (10.1 g, 206 mmol) and the resulting mixture was stirred at room temperature for 18h, then poured into cold water (600 mL) and extracted three times with ether. The organic extract was washed three times with water, once with brine and was dried (potassium carbonate). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with 10% ethyl acetate/hexanes, to provide an off-white solid (17.7 g, 84%): m.p. 32-34°C; an additional quantity (1.3 g) of slightly impure material also was isolated.

- 1b. Dimethyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl) pimelate To a solution of (3-cyclopentyloxy-4-methoxyphenyl)acetonitrile (7 g, 30.3 mmol) in acetonitrile (200 mL) under an argon atmosphere was added a 40% solution of Triton-B in methanol (1.4 mL, 3.03 mmol) and the mixture was heated to reflux. Methyl acrylate (27 mL, 303 mmol) was added carefully, the reaction mixture was maintained at reflux for 5h and then cooled. The mixture was diluted with ether, was washed once with 1N hydrochloric acid and once with brine, was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The solid residue was triturated with 5% ethanol/hexane to provide a white solid (9 g, 74%): m.p. 81-82°C; and additional 1.1 g (9%) was also obtained from the filtrate.

Analysis Calc. for C₂₂H₂₉NO₆: C 65.49, H 7.25, N 3.47; found: C 65.47, H 7.11, N 3.49.

- 1c. 2-Carbomethoxy-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one To a solution of dimethyl 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl) pimelate (5.9 g, 14.6 mmol) in dry 1,2-dimethoxyethane (120 mL) under an argon atmosphere was added sodium hydride (80% suspension in mineral oil, 1.05 g, 43.8 mmol). The mixture was heated to reflux for 4.5h, then was cooled to room temperature and was stirred for 16h. Water was added and the reaction mixture was partitioned between ether and acidic water. The organic extract was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue

was purified by flash chromatography, eluting with 3:1 hexanes/ethyl acetate, to provide a white foam (4.9 g, 93%).

Analysis Calc. for $C_{19}H_{23}NO_3 \cdot 1/4H_2O$: C 67.09, H 6.84, N 3.72; found: C 66.92, H 6.61, N 3.74.

- 5 1d. 4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one A mixture of 2-carbomethoxy-4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one (0.80 g, 2.15 mmol), dimethyl sulfoxide (16 mL), water (1 mL) and sodium chloride (0.8 g) under an argon atmosphere was heated at 140-145°C for 5h. The reaction mixture was cooled and concentrated. The residue was purified by flash chromatography, eluting with 3:1
10 hexanes/ethyl acetate, to provide a yellow solid. Trituration with hexanes/ethyl acetate yielded a white solid (0.52 g, 77%); m.p. 111-112°C.
Analysis Calc. for $C_{19}H_{23}NO_3$: C 72.82, H 7.40, N 4.47; found: C 72.72, H 7.39, N 4.48.

EXAMPLE 2

- 15 Methyl 2-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]acetate
3a. Methyl 4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-ylidene acetate A solution of methyldiethylphosphonate (1.2 mL, 6.68 mmol) in ethylene glycol dimethyl ether (10 mL) was treated with solid sodium hydride (0.22 g, 7.3 mmol, 80% dispersion in mineral oil) at room temperature under an argon atmosphere. After stirring for
20 1.5h, a solution of 4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexanone (1.0 g, 3.34 mmol) was added and the mixture was allowed to stir for an additional 3h. The reaction mixture was partitioned between methylene chloride and water, was extracted twice, was dried (potassium carbonate) and was evaporated to an oil. Purification by flash column chromatography, eluting with 2:1 hexanes/ethyl acetate, provided an oil (0.48 g, 40%).
25 Analysis Calc. for $C_{21}H_{25}NO_4 \cdot 1/8 H_2O$: C 70.51, H 7.12, N 3.92; found: C 70.36, H 7.01, N 3.89.
3b. Methyl 2-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]acetate A solution of methyl 4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-ylidene acetate (0.19 g, 0.52 mmol) in methanol (10 mL) was
30 hydrogenated with 10% palladium on carbon at 50 psi for 3h. The reaction mixture was filtered through Celite, was washed with methylene chloride and was evaporated. Purification by flash column chromatography, eluting with 3:1 hexanes/ethyl acetate, provided an oil (0.16 g, 86%).
Analysis Calc. for $C_{21}H_{27}NO_4$: C 70.56, H 7.61, N 3.92; found: C 70.49, H 7.65, N 3.88.

35

EXAMPLE 3

cis-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methanol

A suspension of methyl 2-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-yl]acetate (0.18 g, 0.52 mmol) in ether (2.0 mL) with

methanol (0.025 mL) and lithium borohydride (0.02 g, 0.78 mmol) was stirred overnight at room temperature under an argon atmosphere. The reaction mixture was partitioned between methylene chloride and acidic water, was extracted three times, was dried (magnesium sulfate) and was evaporated. Purification by flash column chromatography, eluting with 1:1
5 hexanes/ethyl acetate, provided a white solid (0.1 g, 58.5%); m.p. 119-120°C.
Analysis Calc. for C₁₉H₂₅NO₃: C 72.35, H 7.99, N 4.44; found: C 71.96, H 7.90, N 4.33.

EXAMPLE 4

cis-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methylamine
10 A solution of *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methanol (0.05 g, 0.16 mmol) in tetrahydrofuran (1.2 mL) under an argon atmosphere was treated with triphenylphosphine (0.04 g, 0.16 mmol), phthalimide (0.02 g, 0.16 mmol) and then diethylazodicarboxylate (0.03 mL, 0.16 mmol) was added dropwise. The reaction
15 flask was covered with foil and the mixture was stirred at room temperature for 30h. The solvent was evaporated and the residue was purified by flash column chromatography, eluting with 2:1 hexanes/ethyl acetate, to provide the phthalimide (0.06 g, 89.7%), which was dissolved in ethanol (0.5 mL) under an argon atmosphere and refluxed with hydrazine hydrate (0.08 mL, 0.15 mmol) for 3h. The reaction was cooled, the precipitate was removed
20 by filtration, the filtrate was applied to a silica column and the product was eluted with 95:5 chloroform/methanol to provide an oil (0.3 g, 60%).
Analysis Calc. for C₁₉H₂₆N₂O₃·1/4 H₂O: C 71.55, H 8.37, N 8.78; found: C 71.47, H 8.21, N 8.67.

EXAMPLE 5

cis-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methylenoxide
25 To a mixture of 80% sodium hydride in mineral oil (0.06 g, 2.00 mmol) and trimethylsulfonium iodide (0.41g, 2.00 mmol) at room temperature under an argon atmosphere was added dropwise dimethylsulfoxide (4 mL) and the reaction mixture was stirred for 0.5h. A solution of 4-cyano-4-(3-cyclopropylmethoxy-4-
30 methoxyphenyl)cyclohexan-1-one (0.50 g, 1.67 mmol) in dimethylsulfoxide (2 mL) was added and stirring was continued for 45 min. The reaction mixture was quenched with saturated ammonium chloride, was partitioned between ethyl acetate and water, was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography, eluting with 3:7 ethyl acetate/hexanes, to provide a white solid (0.28
35 g, 53%); m.p. 90-91°C.
Analysis Calc. for C₁₉H₂₃NO₃·1/4 H₂O: C 71.79, H 7.45, N 4.41; found: C 71.97, H 7.33, N 4.36.
A small amount of the *trans*-isomer (0.09 g, 17%) was also isolated.

EXAMPLE 6

cis-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexan-1-yl]methanol

A mixture of *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methylenoxide (0.14 g, 0.45 mmol) and potassium hydroxide (0.02 g, 0.36 mmol) in 85:15 dimethylsulfoxide/water (14 mL) under an argon atmosphere was heated at 100-110°C for 1.5h, was cooled, was diluted with water and was extracted three times with ethyl acetate. The organic extract was washed four times with water, once with brine, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 2% methanol/dichloromethane, provided the *cis*-isomer as a white solid (0.09 g, 60%); m.p. 48-50°C.

Analysis Calc. for C₁₉H₂₅NO₄·1/8 H₂O: C 68.39, H 7.63, N 4.20; found: C 68.23, H 7.59, N 4.13.

EXAMPLE 7

trans-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-cyclohexan-1-yl]methylenoxide

To a mixture of 80% sodium hydride in mineral oil (0.33 g, 11 mmol) and trimethylsulfoxonium iodide (1.69 g, 7.67 mmol) at room temperature under an argon atmosphere was added dropwise dimethylsulfoxide (12 mL) and the reaction mixture was stirred for 30 min. A solution of 4-cyano-4-(3-cyclopropylmethoxy-3-methoxyphenyl)-cyclohexan-1-one (2.00 g, 6.68 mmol) in dimethylsulfoxide (5 mL) was added and stirring was continued for 30 min. The reaction mixture was quenched with saturated ammonium chloride, was partitioned between ethyl acetate and water, was dried (magnesium sulfate) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography, eluting with 1:3 ethyl acetate/hexanes, to provide a colorless oil (1.42 g, 68%).

Analysis Calc. for C₁₉H₂₃NO₃·H₂O: C 68.86, H 7.30, N 4.23; found: C 69.22, H 7.11, N 4.17. Starting material was also recovered (0.6 g, 30%).

EXAMPLE 8

trans-[4-Cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexan-1-yl]methanol

A mixture of *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-cyclohexan-1-yl]methylenoxide (1.31 g, 4.18 mmol) and potassium hydroxide (0.14 g, 2.5 mmol) in 85:15 dimethylsulfoxide/water (140 mL) under an argon atmosphere was heated at 100-110°C for 1h, was cooled, was diluted with water and was extracted three times with ethyl acetate. The organic extract was washed five times with water, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 3.5:96.5

methanol/dichloromethane, provided the *trans*-isomer as a sticky white solid: m.p. 38-42°C (0.96 g, 69%).

Analysis Calc. for C₁₉H₂₅NO₄: C 68.86, H 7.60, N 4.23; found: C 68.96, H 7.62, N 4.03.

5

METHODS OF TREATMENT

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof may be used neat though a preferred technique is to present them with a carrier/diluent accordance with standard pharmaceutical practice. Any formulation compatible with the chosen method of delivery and the stability of the compound may be used. One skilled in the art will be able to select and prepare an acceptable formulation in accordance with standard practices in the field of the formulary arts.

The compounds of Formula (I) or may be administered orally (when active by this route), oral, intravenous, intraperitoneal, and intramuscular administration, topically, parenterally, or by inhalation in conventional dosage forms prepared by combining such agent with standard pharmaceutical carriers according to conventional procedures in an amount sufficient to produce the desired therapeutic activity.

The amount of a compound of Formula (I) required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the condition and the animal undergoing treatment, and is ultimately at the discretion of the physician.

The daily dosage regimen for oral administration is suitably about .001 mg/kg to 100mg/kg, preferably 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit activity.

25

UTILITY EXAMPLES

EXAMPLE A

Inhibitory effect of compounds of Formula (I) on *in vitro* TNF production by human monocytes

The inhibitory effect of compounds of Formula (I) on *in vitro* TNF production by human monocytes may be determined by the protocol as described in Badger *et al.*, EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

35

EXAMPLE B

Two models of endotoxic shock have been utilized to determine *in vivo* TNF activity for the compounds of Formula (I). The protocol used in these models is described in Badger *et al.*, EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

The exemplified compounds herein demonstrated a positive *in vivo* response in reducing serum levels of TNF induced by the injection of endotoxin.

EXAMPLE C

Isolation of PDE Isozymes

The phosphodiesterase inhibitory activity and selectivity of the compounds of Formula (I) can be determined using a battery of five distinct PDE isozymes. The tissues used as sources of the different isozymes are as follows: 1) PDE Ib, porcine aorta; 2) PDE Ic, guinea-pig heart; 3) PDE III, guinea-pig heart; 4) PDE IV, human monocyte; and 5) PDE V (also called "Ia"), canine trachealis. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques [Torphy and Cieslinski, Mol. Pharmacol., 37:206-214, 1990]. PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography [Torphy *et al.*, J. Biol. Chem., 267:1798-1804, 1992].

Phosphodiesterase activity is assayed as described in the protocol of Torphy and Cieslinski, Mol. Pharmacol., 37:206-214, 1990. Positive IC₅₀'s in the nanomolar to μ M range for compounds of the workings examples described herein for Formula (I) have been demonstrated.

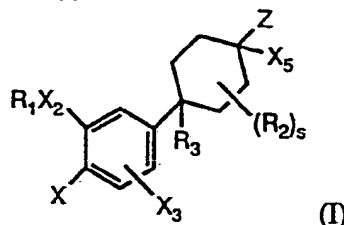
EXAMPLE D

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV inhibition in intact cells, nondifferentiated U-937 cells (approximately 10^5 cells/reaction tube) were incubated with various concentrations (0.01-1000 μ M) of PDE inhibitors for one minute and 1 μ M prostaglandin E₂ for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 17.5% perchloric acid, the pH was neutralized by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A general protocol for this assay is described in Brooker *et al.*, Radioimmunoassay of cyclic AMP and cyclic GMP., Adv. Cyclic Nucleotide Res., 10:1-33, 1979. The compounds of the working examples as described herein for Formula (I) have demonstrated a positive EC₅₀s in the μ M range in the above assay.

No toxic effects are expected when these compounds are administered in accordance with the present invention.

What is claimed is

1. A compound of Formula (I):



wherein:

- 5 R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;
- m is 0 to 2;
- n is 1 to 4;
- 10 r is 1 to 6;
- R_4 and R_5 are independently selected from hydrogen or C_{1-2} alkyl;
- R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxy C_{1-3} alkyl, halo substituted aryloxy C_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranal, tetrahydrothienyl, thienyl, tetrahydrothiopyranal, thiopyranal, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;
- 15 provided that:
- a) when R_6 is hydroxyl, then m is 2; or
- 20 b) when R_6 is hydroxyl, then r is 2 to 6; or
- c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or
- d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranal, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;
- 25 e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;
- X is YR_2 , halogen, nitro, NR_4R_5 , or formyl amine;
- Y is O or $S(O)_{m'}$;
- m' is 0, 1, or 2;
- X_2 is O or NR_8 ;
- 30 X_3 is hydrogen or X;
- R_2 is independently selected from $-CH_3$ or $-CH_2CH_3$ optionally substituted by 1 or more halogens;
- s is 0 to 4;

R₃ is hydrogen, halogen, C₁₋₄ alkyl, CH₂NHC(O)C(O)NH₂, halo-substituted C₁₋₄ alkyl, -CH=CR₈R₈', cyclopropyl optionally substituted by R₈', CN, OR₈, CH₂OR₈, NR₈R₁₀, CH₂NR₈R₁₀, C(Z')H, C(O)OR₈, C(O)NR₈R₁₀, or C≡CR₈';

Z' is O, NR₉, NOR₈, NCN, C(-CN)₂, CR₈CN, CR₈NO₂, CR₈C(O)OR₈,
5 CR₈C(O)NR₈R₈, C(-CN)NO₂, C(-CN)C(O)OR₉, or C(-CN)C(O)NR₈R₈;

Z is CR₈R₈OR₁₄, CR₈R₈OR₁₅, CR₈R₈SR₁₄, CR₈R₈SR₁₅, CR₈R₈S(O)_mR₇,
CR₈R₈NR₁₀R₁₄, CR₈R₈NR₁₀S(O)₂NR₁₀R₁₄, CR₈R₈NR₁₀S(O)₂R₇,
CR₈R₈NR₁₀C(Y')R₁₄, CR₈R₈NR₁₀C(O)OR₇, CR₈R₈NR₁₀C(Y')NR₁₀R₁₄,
CR₈R₈NR₁₀C(NCN)NR₁₀R₁₄, CR₈R₈NR₁₀C(CR₄NO₂)NR₁₀R₁₄,
10 CR₈R₈NR₁₀C(NCN)SR₉, CR₈R₈NR₁₀C(CR₄NO₂)SR₉, CR₈R₈C(O)OR₁₄,
CR₈R₈C(Y')NR₁₀R₁₄, CR₈R₈C(NR₁₀)NR₁₀R₁₄, CR₈R₈CN, CR₈R₈(tetrazolyl),
CR₈R₈(imidazolyl), CR₈R₈(imidazolidinyl), CR₈R₈(pyrazolyl), CR₈R₈(thiazolyl),
CR₈R₈(thiazolidinyl), CR₈R₈(oxazolyl), CR₈R₈(oxazolidinyl), CR₈R₈(triazolyl),
CR₈R₈(isoxazolyl), CR₈R₈(oxadiazolyl), CR₈R₈(thiadiazolyl), CR₈R₈(morpholinyl),
15 CR₈R₈(piperidinyl), CR₈R₈(piperazinyl), CR₈R₈(pyrrolyl), CR₈R₈C(NOR₈)R₁₄,
CR₈R₈C(NOR₁₄)R₈, CR₈R₈NR₁₀C(NR₁₀)SR₉, CR₈R₈NR₁₀C(NR₁₀)NR₁₀R₁₄,
CR₈R₈NR₁₀C(O)C(O)NR₁₀R₁₄, or CR₈R₈NR₁₀C(O)C(O)OR₁₄;

X₅ is H, OR₈, CN, C(O)R₈, C(O)OR₈, C(O)NR₈R₈, or NR₈R₈; or Z and X₅ together is -CR₈R₈O-;

20 Y' is O or S;

R₇ is -(CR₄R₅)_qR₁₂ or C₁₋₆ alkyl wherein the R₁₂ or C₁₋₆ alkyl group is optionally substituted one or more times by C₁₋₂ alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, -NO₂, -NR₁₀R₁₁, -C(O)R₈, -C(O)OR₈, -OR₈, -CN, -C(O)NR₁₀R₁₁, -OC(O)NR₁₀R₁₁, -OC(O)R₈, -NR₁₀C(O)NR₁₀R₁₁, -NR₁₀C(O)R₁₁, -NR₁₀C(O)OR₉,
25 -NR₁₀C(O)R₁₃, -C(NR₁₀)NR₁₀R₁₁, -C(NCN)NR₁₀R₁₁, -C(NCN)SR₉,
-NR₁₀C(NCN)SR₉, -NR₁₀C(NCN)NR₁₀R₁₁, -NR₁₀S(O)₂R₉, -S(O)_mR₉,
-NR₁₀C(O)C(O)NR₁₀R₁₁, -NR₁₀C(O)C(O)R₁₀, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

30 R₁₂ is C₃₋₇ cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;

R₈ is independently selected from hydrogen or R₉;

R₈' is R₈ or fluorine;

35 R₉ is C₁₋₄ alkyl optionally substituted by one to three fluorines;

R₁₀ is OR₈ or R₁₁;

R₁₁ is hydrogen, or C₁₋₄ alkyl optionally substituted by one to three fluorines; or when R₁₀ and R₁₁ are as NR₁₀R₁₁ they may together with the nitrogen form a 5 to 7

membered ring optionally containing at least one additional heteroatom selected from O, N, or S;

R₁₃ is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these
 5 heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C₁₋₂ alkyl groups;

R₁₄ is hydrogen or R₇; or when R₁₀ and R₁₄ are as NR₁₀R₁₄ they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;

10 R₁₅ is C(O)R₁₄, C(O)NR₈R₁₄, S(O)₂NR₈R₁₄, S(O)₂R₇;

provided that:

f) when R₁₂ is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1;

g) when X₂R₁ is OCF₂H or OCF₃, X is F, OCF₂H or OCF₃, X₃ is H, s is zero, X₅
 15 is H, Z is CH₂OR₁₄, and R₁₄ is C₁₋₇ unsubstituted alkyl, then R₃ is other than H;
 or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is:

methyl 2-[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-yl]acetate;

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methanol;

20 *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1-yl]methylamine;

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1,1-diyl]oxirane;

cis-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexan-1-yl]methanol;

25 *trans*-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)cyclohexan-1,1-diyl]oxirane; or

trans-[4-cyano-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-1-hydroxycyclohexan-1-yl]methanol.

30 3. A pharmaceutical composition comprising a compound of Formula (I) according to claim 1 and a pharmaceutically acceptable excipient.

4. A method for treating an allergic or inflammatory state which method comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) according to claim 1 alone or in combination with a pharmaceutically acceptable
 35 excipient.

INTERNATIONAL SEARCH REPORT

PCT/US93/01988

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/275; C07C 255/50

US CL :514/521; 558/426

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/521; 558/426 514/475; 549/332

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Chemical Abstracts Structure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts, 08 July 1991, Solomina et al. Abstract No. 115:85425 See formula II	1-3
X	Chemical Abstracts, 12 March 1979, Agekyan et al. Abstract No. 90:86895p See formula III.	1-3
X	Chemical Abstracts, 04 July 1983, Agekyan et al. Abstract No. 99:5272u See formula I	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be part of particular relevance	X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	Z	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
24 JUNE 1993	23 JUL 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer JACQUELINE HALEY
Facsimile No. NOT APPLICABLE	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01988

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

Each of the following groupings of inventions is drawn to compounds, compositions and methods of use and is defined according to compound structure.

- I. Claims 1 and 3-4 (each in part), wherein the compound contains nitrogen-containing heterocycles, Classes 540, 544, 546, 548 and 514, subclasses various.
- II. Claims 1 and 3-4 (each in part), wherein the compound contains none of group I above and contains sulfur-containing heterocycles, Classes 549 and 514, subclasses various.
- III. Claims 1-4 (each in part), wherein the compound contains none of groups 1-2 above and contains oxygen-containing heterocycles, Classes 514, 549, subclasses various.
- IV. Claims 1 and 3-4 (each in part), wherein the compound contains none of groups 1-3 above and wherein the compound has at least one $-\text{SO}_2\text{-O-C}$ group, Class 558, subclass 44+ and the corresponding Class 514 subclasses.
- V. Claims 1 and 3-4 (each in part), wherein the compound contains none of the groups 1-4 above and wherein the compound has at least one $-\text{C(X)-X-}$ group (wherein one X is sulfur), Class 558, subclass 230+ and the corresponding Class 514 subclasses.
- VI. Claims 1-4 (each in part), wherein the compound contains none of the groups 1-5 above and wherein the compound has at least one $-\text{CN}$ group, Class 558, subclass 388+ and the corresponding Class 514 subclasses.
- VII. Claims 1 and 3-4 (each in part), wherein the compound contains none of the groups 1-6 above and wherein the compound has at least one C-CO-O-C group, Class 560, subclasses 1+ and the corresponding Class 514 subclasses.
- VIII. Claims 1 and 3-4 (each in part), wherein the compound contains none of the groups 1-7 above and wherein the compound has at least one $\text{N-SO}_2\text{-S-R}$ group, Class 560, subclasses 307+ and corresponding Class 514 subclasses.
- IX. Claims 1 and 3-4 (each in part) wherein the compound contains none of the groups 1-8 above and wherein the compound has at least one group $-\text{COOH}$, Class 562, subclasses 400+ and corresponding 514 subclasses.
- X. Claims 1 and 3-4 (each in part) wherein the compound contains none of groups 1-9 above and wherein the compound has at least one group $-\text{N-CS-N}$, Class 564, subclass 17+ and the corresponding 514 subclasses.
- XI. Claims 1 and 3-4 (each in part) wherein the compound contains none of the groups 1-10 above wherein the compound has at least one group $-\text{N-CO-N-}$, Class 564, subclass 32+ and the corresponding 514 subclasses.
- XII. Claims 1 and 3-4 (each in part), wherein the compounds contain none of the groups 1-11 above and wherein the compounds have at least one N-CS-group , Class 564, subclasses 74+ and the corresponding 514 subclasses.
- XIII. Claims 1 and 3-4 (each in part), wherein the compounds contain none of the groups 1-12 above and wherein the compound has at least one group $-\text{N-SO}_2\text{-N}$, Class 564, subclass 79+ and the corresponding 514 subclasses.
- XIV. Claims 1 and 3-4 (each in part) wherein the compounds contain none of the groups 1-13 above and wherein the compound has at least one group N-CO-R , Class 564, subclasses 123+ and the corresponding 514 subclasses.
- XV. Claims 1 and 3-4 (each in part), wherein the compound contains none of groups 1-14 above and wherein the compound has at least one group $-\text{NH-}$, i.e. amino nitrogen group, Class 564, subclass 225+ and the corresponding 514 subclasses.
- XVI. Claims 1 and 3-4 (each in part), wherein the compound contains none of the group 1-15 above and wherein the compound has at least one group $-\text{N-OH}$ or $-\text{N-OR}$, Class 564, subclass 300+ and the corresponding 514 subclasses.

INTERNATIONAL SEARCH REPORT

International application No.

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XVII. Claims 1 and 3-4 (each in part), wherein the compound contains none of the groups 1-16 above and wherein the compound has at least one -SH or -R-S-R- group, Class 568, subclasses 38-61 and the corresponding 514 subclasses.

XVIII. Claims 1 and 3-4 (each in part), wherein the compound contains none of the groups 1-17 above and wherein the compound contains at least one aldehyde group, Class 568 and subclass 420+ and the corresponding 514 subclasses.

XIX. Claims 1 and 3-4 (each in part), wherein the compound contains none of the groups 1-18 above and at least one R-O-R group, Class 568, subclass 579+ and the corresponding 514 subclasses.

The application lacks unity of invention under PCT Rule 13.1-13.4 since the cyclohexyl phenyl group is not seen to be a technical feature which defines over the prior art.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01988

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1,3-4 (each in part); claim 2 (in its entirety). It is deemed that the first claimed invention is the first species of claim 2

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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